Background: The Eastern Co-operative Oncology Group (ECOG) 4599 phase III trial demonstrated that the addition of bevacizumab to carboplatin/paclitaxel (CP) significantly improved overall survival and progression-free survival (PFS) in patients with advanced non-squamous non-small cell lung cancer (NSCLC) [Sandler et al., NEJM 2006;355:2542-50]. Cisplatin/gemcitabine (CG) is a combination commonly used in Europe and other regions outside of the USA. In order to establish the efficacy of bevacizumab in combination with cisplatin-based doublets, the BO17704 trial investigated the effect of the addition of bevacizumab to CG on PFS in patients with advanced NSCLC.

Methods: This randomised, placebo-controlled, multicentre 3-arm phase III study compared the efficacy of two doses of bevacizumab in combination with CG versus CG plus placebo. The primary endpoint was to demonstrate superiority in PFS in both bevacizumab-containing treatment arms versus the control regimen. Secondary endpoints were overall survival, response rate and safety. Eligibility criteria were histologically or cytologically documented previously untreated locally advanced, metastatic or recurrent non-squamous NSCLC; ECOG performance status 0-1; adequate haematological, renal and liver function; no brain metastases; no history of recent CTC grade ≥2 haemoptysis. Between February 2005 and August 2006, a total of 1,043 patients were randomised 1:1:1 to three treatment groups. One group received up to 6 cycles of C 80mg/m^2 on day 1 and G 1,250mg/m^2 on day 1 and day 8 every 3 weeks plus placebo (n=347). The second group received CG chemotherapy plus bevacizumab at a dose of 7.5mg/kg every 3 weeks (n=345), and the third group received CG chemotherapy plus bevacizumab at a dose of 15mg/kg every 3 weeks (n=351). Bevacizumab was to be administered until disease progression for both bevacizumab arms. Data cut-off was two months after the last patient was enrolled.

Results: Bevacizumab at a dose of 7.5 or 15mg/kg every 3 weeks in combination with CG chemotherapy significantly prolonged PFS in patients with advanced NSCLC when compared with CG chemotherapy plus placebo. The treatment effects observed in the two bevacizumab-containing arms were similar. No new safety signals associated with the use of bevacizumab were observed for either bevacizumab dose in this clinical setting.

Conclusions: The trial met its primary endpoint. Final efficacy and safety results for each arm will be presented at the meeting.

C1-07 Molecular Targeted Therapy: Beyong EGFR, Wed, 10:30 - 12:15

IPI-504, a novel HSP90 inhibitor is effective in EGFR T790M and Non-T790M Gefitinib-resistant Lung Cancer Cell Lines.

Park, Joon Oh[1] Zhao, Feng[1] Zejnullahu, Kreshnik[1] Normant, Emmanuel[2] Engelman, Jeffrey A.[3] Johnson, Bruce E.[1] Jänne, Pasi A.[1]

[1] Dana-Farber Cancer Institute, Boston, MA, USA [2] Infinity Pharmaceuticals, Inc., Cambridge, MA, USA [3] Massachusetts General Hospital Cancer Center, Boston, MA, USA

Background: Acquired resistance to gefitinib in NSCLC patients with somatic activating EGFR mutations has been associated with the development of a secondary T790M mutation in about 50% of the patients. The mechanisms for acquired resistance in the remaining tumors are still unknown. Heat shock protein 90 (Hsp90) is a molecular chaperone that plays a key role in the conformational maturation of oncogenic signaling proteins and has become an exciting therapeutic target for the treatment of cancer. IPI-504, the highly soluble hydroquinone hydrochloride derivative of 17-AAG, was synthesized as an Hsp90 inhibitor with favorable pharmaceutical properties. Herein, we explored new therapeutic strategies overcoming the EGFR T790M and non-T790M gefitinib-resistance mechanisms. Methods and Results: We have developed gefitinib-resistant (GR) clones from gefitinib-hypersensitive EGFR L858R mutant (H3255) and EGFR exon 19 deletion (del E746_A750) mutant (HCC827) NSCLC cell lines by exposing them to increasing concentrations of gefitinib in vitro. Analyses of the resistant cells demonstrate that H3255 GR contain an EGFR T790M mutation which is not observed in HCC827 GR cells. We investigated the effects of IPI-504 on cells according to the mechanism of resistance to gefitinib; KRAS mutation (A549 and H441), EGFR T790M mutation (H1975 and H3255GR) and non-T790M mutation (HCC827GRs). In time course experiments, mutant EGFR proteins in H1975, H3255GR and HCC827GRs were depleted after only 6 hrs of exposure to 100 nM IPI-504, while diminution of wild-type EGFR in A549 and H441 was less substantial. However, several client proteins for Hsp90 were equally affected among these cell lines. Exposure to IPI-504 showed dose and time dependent growth inhibition exhibiting IC50 values for cell viability at 72 h that ranged from 41 - 293nM. All cell lines tested were found to be sensitive to IPI-504 regardless of gefitinib-resistance mechanisms. When gefitinib was combined, IPI-504 also showed synergism with Combination Indices (CI) at the IC50 and further studies are ongoing to evaluate for potential synergy with gefitinib. Flow cytometric Tunel assay and fluorescent-based casspase 3/7 in H1975, H3255GR and HCC827GR with mutant EGFR showed that the 48 hr treatment with 1.0uM IPI-504 caused an increase in sub-G1 fraction and apoptosis.

Conclusions: These data support the conclusion that mutational activation of EGFR is associated with dependence on Hsp90 for stability. Taken together, IPI-504 represents a novel strategy for the treatment of NSCLC patients having EGFR T790M or non-T790M gefitinib-resistance mechanism and suggests an important implication for clinical development.

Session C2: Staging Efficacy
Wednesday, September 5

C2-01 Staging Efficacy, Wed, 10:30 - 12:15

Endobronchial ultrasound with transbronchial needle aspiration for restaging the mediastinum

Herth, Felix J.[1] Ernst, Armin[2] Yasufuku, Kazu[3] Annema, Jouke[4] Rintoul, Robert[5] Krasnik, Mark[6]

[1] Thoraxklinik Heidelberg, Heidelberg, Germany [2] BIDMC, Harvard Medical School, Boston, MA, USA [3] Depatment of Thoracic Surgery, Chiba University, Chiba, Japan [4] University of Leiden, Leiden, The Netherlands [5] Papworth Hospital, Cambridge, UK [6] Depp. Of Thoraqcic Surgery, Copenhagen, Denmark

Study Objective: Protocols using indction chemotherapy for advanced lung cancer are more frequently used with the hope that surgery can be performed after the cancer is downstaged. The current restaging modalities either have a low diagnostic accuracy (computed tomography) or can be technically difficult (Re-, mediastinoscopy). Endobronchial ultrasound guided TBNA is an excellent tool for mediastinal lymph node staging and may have a role in restaging also.

Methods and Patients: Patients with NSCLC and proven ipsilateral or subcarinal lymph node metastases (N2 disease, 3A disease stage) who had been treated with induction chemotherapy and showing at least stable disease or partial response on CT imaging underwent mediastinal restaging by EBUS-TBNA. This was followed by surgical resection of the tumour with lymph node dissection.

Results: 124 Patients (51 male, 73 female, mean age 58 y.) had either a partial response (n=66) or stable disease (n=58) based on sequential CT scans of the thorax. After restaging all patients underwent surgery. Overall the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of EBUS-TBNA for mediastinal re-staging following induction chemotherapy were 76%, 100%, 100%, 20% and 77% respectively.

Conclusions: EBUS-TBNA is an accurate, safe and minimally invasive diagnostic technique for the restaging of mediastinal lymph nodes after induction therapy in NSCLC. It's routine use for this purpose should be considered.

C2-02 **Staging Efficacy, Wed, 10:30 - 12:15**

Factors effecting risk of pneumothorax (PNX) in CT-guided transthoracic needle biopsy of lung lesions: results of 708 consecutive procedures

Priola, Adriano M.[1] Novello, Silvia[2] Priola, Sandro M.[1] Longo, Marina[3] Cataldi, Aldo[1] Errico, Luca[4] Garofalo, Giorgio[1] Giaj Levra, Matteo[3] Scagliotti, Giorgio V.[3] Fava, Cesare[1]

[1] University of Turin, Radiology Dept, Orbassano, Italy [2] University of Turin, Orbassano, Italy [3] University of Turin, Thoracic Oncology Dept, Orbassano, Italy [4] University of Turin, Thoracic Surgery, Orbassano, Italy

Background: CT-guided Transthoracic Needle Biopsy (TNB) is commonly used in the diagnosis of thoracic lesions. PNX is the most common complication of this procedure with a reported rate from 8 to 61%, with few cases requiring chest tube insertion. The aim of this prospective study was to estimate the risk of PNX in patients undergoing CT-guided lung biopsy and to determine which factors affect its occurrence.

Methods: Between November 2002 and August 2006, 708 TNB were performed in 691 patients with a CT-documented central or peripheral pulmonary lesion: 75% were males, median age was 67 years (range 29-87). Risk factors for PNX were classified in three groups: patient-related (age, sex, emphysema around the lesion), lesion-related (size, depth, location, presence of cavitations and/or pleural tags, chest wall invasion, pleural thickening, fissure/atelectasis in the needle path) and procedure-related (patient position, needle puncture side, chest wall thickness, dwell-time (time between pleural puncture and needle removal), needle-pleural angle (smallest angle of the needle with the pleura), number of cutting specimens, number of pleural passages. Lesion depth was measured as the length of the aerated lung from the surface of pleura to the edge of the lesion. Lesion size was considered the average lesion diameter in two axial planes. Immediately after the procedure, a CT scan was obtained to control presence of PNX; patients were followed-up for 4 hours and chest radiographs were obtained at the end of this period. All variables were analysed by Chi-square and Student t test for occurrence of PNX and p value < 0.05 was considered as statistically significant.

Results: PNX occurred in 181/708 procedures (25.6%) and tube insertion was required in 18 cases (2.5%). An higher lesion depth was the most significant predictor of PNX (p=0.002): the mean depth of lesions from the pleural surface was 27.4 mm in patients with PNX and 17.2 mm in patients without PNX. There were 216 lesions in direct contact with the pleura: PNX developed in only 20 (9.2%). Among lesion related variables, chest wall invasion (p<0.03) and lesion size (p=0.03; 31.7 mm in group with vs 38.9 mm in group without PNX) showed correlation. A greater incidence of PNX was seen in smaller lesions: for lesions 1 cm or smaller, the rate was 35%. Among patient and procedure variables, age (68 vs 64 years, p<0.03) and number of cutting specimens (p=0.01) were associated with an increased risk of PNX. Number of pleural punctures, needle-pleural angle, dwell-time, lesion location, presence of emphysema along needle path and sex did not effect risk of PNX.

Conclusion: In consecutive cases of CT-guided TNB the length of the lung parenchyma crossed during the biopsy is the predominant risk factor for PNX. The risk of PNX was also related to the mean lesion size, age, presence of chest wall invasion and number of cutting specimens.

C2-03 **Staging Efficacy, Wed, 10:30 - 12:15**

The accuracy of real-time endobronchial ultrasound (EBUS) in the staging of lung cancer

Skwarski, Kristopher M.[1] McCafferty, John[2] Wood, Fraser[3] Wallace, William[2] Murray, Maeve[2] Chalmers, James[2] Matthews, Jennifer[2]

[1] Respiratory Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK [2] The Royal Infirmary of Edinburgh, Edinburgh, UK [3] St John's Hospital, Livingstone, Edinburgh, UK

Accurate staging allows assessment of prognosis and determines treatment plans in patients with lung cancer. Evaluation of mediastinal lymphnodes (LN) is crucial to determine the stage of the cancer. Only up to 20% of patients with lung cancer present in early stage allowing surgical treatment. Current mediastinal staging methods include mediastinoscopy (MS) and CT-PET. MS with the sensitivity of 70% - 95% is the gold standard in evaluation of LN and provides access to LN stations: 2, 3, 4, and 7. MS is an invasive procedure, which requires general anaesthetic, carries minimal, nonetheless, mortality and for technical reasons it is usually done only once. There is therefore a need to develop less invasive techniques allowing an adequate evaluation of mediastinal LN. CT-PET has been shown to be useful in predicting malignant mediastinal LN with a high negative predictive value (97%) but with only moderate positive predictive value (75%). However, CT-PET does not provide histological diagnosis. Real-time Endobronchial Ultrasound FNA with Doppler facilities (EBUS) provides a safe alternative to MS in staging of lung cancer. EBUS allows easy access to mediastinal and hilar LN stations: 2, 3, 4, 7, 10 and 11. EBUS is performed as an out-patient procedure in conjunction with standard bronchoscopy under conscious sedation.

We have performed 300 EBUS procedures from May 2005 until Mar 2007 using an OLYMPUS Ultrasonic Linear Bronchoscope BF-UM40. Tissue samples were obtained using 22G needle and processed using a thin layer technique and stained with PAP. Any residual material was processed as a cell block.

There were 153 positive aspirations for malignancy. In 124 cases we diagnosed Non Small Cell Lung Cancer, 23 Small Cell Lung Cancer and 6 mixed tumours. The most frequently (in order) sampled LN stations were: 7, 4, 10, 11, 2 and 3. There were 7 false negative results. 87 primary tissue diagnoses were obtained and 137 MS were avoided. There were no complications. Calculated EBUS sensitivity was 94%